EXHIBIT AA

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC. PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL No. 2327**
THIS DOCUMENT RELATES TO WAVE I	**JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

GENERAL EXPERT

REPORT OF DANIEL J. SEXTON, M.D.,

REGARDING TVT AND TVT-O

Prepared by

Daniel J. Sexton, M.D.
Duke University
Durham, NC 27710
February 24, 2016

I. BACKGROUND AND QUALIFICATIONS

I am a Professor in the Department of Medicine and the Division of Infectious Diseases at Duke University Medical Center in Durham, North Carolina, and a physician licensed to practice medicine in North Carolina. A copy of my Curriculum Vitae is attached hereto as Exhibit A.

The materials I reviewed and relied on in reaching the opinions set forth in this report are listed in Exhibit B. A list of all other cases in which I have testified in the previous four years is attached as Exhibit C. My compensation for my review and input in this legal matter will be billed at a rate of $600/hour. My rate for providing testimony by deposition is $750/hour.

I received my medical degree from Northwestern University in 1971 and am certified by the American Board of Internal Medicine in the fields of Internal Medicine and Infectious Diseases. I am a Fellow in the American College of Physicians, the Society for Healthcare Epidemiology of America, and the Infectious Diseases Society of America. I estimate that during a clinical career as an infectious diseases consultant of greater than 35 years, I saw more than 20,000 patients with infections in consultation. As pertinent here, these consultations included thousands of patients with infections that developed after surgical implantation of prosthetic valves, joints, pacemakers, vascular grafts, mesh grafts, and orthopedic hardware.

I have received the Clinician Award from the Infectious Diseases Society of America (IDSA) and was previously the Chair of the IDSA Clinical Affairs Committee and served three-year terms on the IDSA Board of Directors and the National Foundation for Infectious Diseases. I received the Golden Apple Teaching Award from the Duke University School of Medicine, a Golden Apple Award from the American Medical School Student Association, and the Eugene

Stead Award for Excellence in Teaching from the Duke Medicine House staff (twice). In 2011, I was named a Master Clinician Teacher by the Duke University School of Medicine. In 2015 I received the Senior Scholarship Award from the Society for Healthcare Epidemiology of America. I have written over 220 peer-reviewed articles and editorials in the field of infectious diseases; authored more than 60 book chapters; and presented scientific papers and lectured on infectious diseases and hospital-acquired infections both nationally and internationally. I am a senior editor of the infectious diseases section of the on-line textbook UpToDate. I have had a direct role in the research training of hundreds of medical students and residents, and approximately 100 fellows. I was the supervising mentor for 14 infectious diseases fellows who are currently working in academic medical centers as hospital epidemiologists. I am currently the supervisor for 2 additional infectious diseases fellows who are pursuing careers in infection control and hospital epidemiology. I was a member of the Infection Control Committee at numerous hospitals from 1981 to 2014 and Chairman of the Infection Control Committee at Duke University Medical Center from 1990-2013.

I am also the director of the Duke Infection Control Network (DICON), a consortium of 43 hospitals in Virginia, North Carolina, Georgia, West Virginia, Michigan, and Florida. Among other things, this network monitors and compares rates of post-operative surgical infections between and among the participating hospitals; provides uniform guidelines, policies, and procedures related to infection control; and investigates increased rates or clusters of infections. Through DICON, I also consult with the National Football League on infection control.

Finally, in conjunction with my work as an infectious disease specialist, I am also a trained epidemiologist. I worked for two years as a medical epidemiologist for the Centers for Disease Control in Atlanta, Georgia, and have maintained an active interest in the clinical

epidemiology of infectious diseases. In my daily work as an infectious disease specialist, I frequently use epidemiological principles and I regularly consult with other epidemiologists on a variety of projects.

II. ISSUES

I have been asked to opine on the following infectious disease issues related to the implantation of the TVT devices (TVT and TVT-O) for the treatment of stress urinary incontinence (SUI):

a. To assist the Court and jury in understanding the medical and scientific principles related to surgical site infections, urinary tract infections, and vaginal infections;

b. To inform the Court and jury of the surgical infection rate accompanying the implantation of a TVT or TVT-O device and to assist the Court and jury in understanding what this rate means;

c. To compare the surgical infection rate associated with the implantation of a TVT or TVT-O device and the comparable rates for alternative surgical procedures for the treatment of SUI, including the Burch colposuspension and the pubovaginal sling;

d. To compare the rates of vaginal yeast and urinary tract infections following implantation of a TVT or TVT-O device and other treatments for SUI;

e. To address several infection-related assertions raised in the reports prepared by the Plaintiffs' experts in these cases, including the assertion that the TVT or TVT-O device is intrinsically unsafe due to its method of implantation; that "colonization" or "biofilms" make TVT or TVT-O unsafe; that women implanted with a TVT or TVT-O are subject to an excessive

risk of "subclinical" or "chronic" infections; and that these subclinical infections will develop into "late infections" or cause other complications years after implantation.

III. SUMMARY OF OPINIONS

I am an expert in the field of infectious diseases, and I make this report in connection with the Wave 1 cases pending in MDL No. 2327 in the Southern District of West Virginia. I hold all opinions expressed in this report to a reasonable degree of medical certainty.

TVT and TVT-O are both mid-urethral polypropylene slings manufactured by Ethicon. The two devices are similar with the principal difference being that TVT exits through the patient's lower abdomen while TVT-O exits through the obturator route. During this report I will frequently refer to the TVT and TVT-O devices as simply "the TVT device" or simply "TVT." In regard to infection related issues, TVT and TVT-O are virtually identical. For example, in a recent metaanalysis the rate of wound infection for the retropubic SUI devices (such as TVT) was found to be 0.75% and transobturator SUI devices (such as TVT-O) was found to be 0.74%. [See Table 3, Schimpf, et al., Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis, Am J Obstet Gynecol 2014; 210: 1.e7-8].

In summary, my opinions in this matter are that: (a) the rate of surgical infection following the implantation of a TVT or TVT-O device is low; (b) the rate of surgical infection associated with the implantation of a TVT or TVT-O device is lower than the comparable rate for the prior gold standard treatment for SUI, the Burch colposuspension, and lower than the comparable rate following implantation of a pubovaginal sling; and (c) the rates of urinary tract infections and vaginal yeast infections in women undergoing implantation of a TVT or TVT-O device are comparable to the rates for women undergoing the Burch colposuspension and

pubovaginal sling. Additionally, in part C of Section IV below, I address and rebut several infection-related issues raised by Plaintiffs' experts.

IV. OPINIONS

A. General Principles Regarding Infectious Disease Issues Applicable to TVT and TVT-O

1. All surgical procedures carry the risk of infection

All surgical procedures at all body sites have risks that include infection. This is true of the Burch colposuspension and every other surgical treatment of SUI. Implanted prosthetic devices such as heart valves, artificial joints, orthopedic hardware and synthetic mesh grafts pose inherent risks. However, surgical implantation of such prosthetic devices also can provide critically important benefits to patients and significantly improve their quality of life.

The preceding risks and benefits of surgery and of using prosthetic devices are typically and reasonably assessed by measuring outcomes of patients who undergo surgery and by comparing outcomes of patients who undergo similar and different procedures using similar or different prosthetic devices. Because the underlying health and characteristics of patients also vary substantially, the preceding comparative process is complex. As a practical matter, each decision about whether the benefits of a specific surgical procedure or prosthetic device justify the risks must be made on a case-by-case basis by surgeons and their patients based on unique and individual circumstances.

It is impossible to perform any surgical procedure or implant any prosthetic device without some degree of intraoperative contamination. Indeed, bacteria are always present in the air of operating rooms, on the skin of patients, or on their mucosal linings. Thus some degree of contamination is inevitable each time any surgery is performed, including the implantation of a

heart valve, prosthetic joint or other orthopedic hardware, vascular grafts, or mesh grafts. However, patients have complex and highly effective immune systems that usually (but not invariably) prevent the subsequent development of an active infection, despite such contamination. This matter will be further discussed later in this report.

The medical literature related to risks of surgery after placement of prosthetic materials is exceedingly complex. As a result, decisions about the relative safety and advisability of using a specific prosthetic material or method of insertion in a specific patient must include consideration of many factors. Simplistic citing of theoretical musings or of isolated facts from studies involving mesh implants of various types in experimental animals such as rats or dogs, in vitro experimental and histological studies, a single study from a single center, or even a series of small studies can lead to misrepresentations of reality. Such information cannot replace or supersede outcome data in humans involved in comparative clinical trials as discussed further in the section below on evidence-based medicine.

The risk of infection related to implanting a prosthetic or synthetic device in humans has to be balanced with efficacy and the risk of alternate surgical procedures or the consequences of not undergoing surgical intervention. For example, despite a known risk of infection, mesh grafts are now the standard technique for hernia repairs in the United States. The basic reason that mesh grafts are now the standard method to repair hernias in the United States is that mesh graft repair of some types of hernia has important advantages over other surgical methods that have other adverse aspects. Specifically, use of such mesh grafts in certain types of hernias and certain types of patients is associated with a lower recurrence rate and a shorter length of hospital stay compared to non-mesh hernia repairs [Mavros MN, Althanasiou S, Alexiou VG et al., Risk factors for mesh-related infections after hernia repair surgery: a meta-analysis of cohort studies,

World J Surg 2011, citations 1, 5-9]. Indeed, it is estimated that more than 1,000,000 such operations are performed annually in the United States [Rutkow IM, Demographic and socioeconomic aspects of hernia repair in the United States in 2003. Surg Clin North Am 2003; 83:1045-51]. In other words, the consensus opinion is that, for most patients, the benefits of mesh repair for many types of hernias *outweigh* the inherent risk of infection when mesh grafts are utilized. These findings and the preceding principles need to be kept in mind in the discussion that follows.

2. Issues affecting measurement of a crude infection rate

As discussed in greater detail below, my review of the available medical literature leads me to conclude that the actual overall or crude rate of post-operative infection following the implantation of the TVT device is lower than the rate of documented post-operative infection following traditional surgical treatments for women suffering from stress urinary incontinence. In order to speak sensibly about infection issues, however, it is important to understand the definition of what is and is not an infection and to provide some context as to how a specific crude infection rate for one procedure relates to crude infection rates for other commonly-performed and widely-accepted surgical procedures.

a. CDC/NHSN Criteria

The Centers for Disease Control and Prevention (CDC) and its National Healthcare Safety Network (NHSN) developed specific criteria for defining whether a post-operative surgical site infection has occurred. These definitions are based on a combination of clinical and laboratory findings. Post-operative surgical site infections can be superficial (incisional), deep (below fascial planes) or in the organ space (i.e. in anatomical spaces below the incision where

they usually manifest as a discrete abscess). Superficial incisional infections can occur at the primary incision or at secondary incision in cases in which two or more incisions are made (as occurs in certain procedures such as coronary artery bypass graft procedures). These definitions specifically exclude both localized stitch abscesses related to suture penetration and localized stab wound infections near device-placement sites such as drains and catheters. Diagnosis of superficial incisional infections requires at least one of the following criteria:

- Purulent drainage from the superficial incision.
- Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
- Superficial incision that is deliberately opened by a surgeon or attending physician and is culture positive or not cultured and the patient has at least 1 of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat.
- A diagnosis of superficial incisional SSI (surgical site infection) by the surgeon or attending physician.

The preceding CDC definitions also have special aspects that relate to surgical site post-operative infections involving the female reproductive tract. For example, surgical site infections after episiotomy procedures require the presence of one of two specific criteria: purulent drainage from the episiotomy incision or an abscess at the site of the episiotomy. Also vaginal cuff infections must have one or more of the following criteria present: (1) purulent drainage from the vaginal cuff, (2) a visible abscess at the vaginal cuff, or (3) pathogens obtained from fluid or tissue obtained at the vaginal cuff.

Moreover, under the latest CDC/NHSN definitions, infections following the implantation of prosthetic materials are attributed to the surgical procedure in which the materials were implanted only if the infection occurs within 90 days of the actual procedure. This standard reflects the fact that infections associated with prosthetic devices that manifest more than 90 days

after implantation of prosthetic materials are uncommon in clinical practice. Additionally, implanted prosthetic devices and materials such as mesh may occasionally become secondarily infected due to conditions unrelated to the original surgical procedure. For example, infections in contiguous tissues, anatomic regions, or in the bloodstream can secondarily infect prosthetic devices implanted years earlier. This is generically true for any prosthetic device after surgical placement.

A positive culture is, in itself, insufficient to make a diagnosis of a post-operative infection unless this finding is accompanied by other bona fide findings of infection as specified in the CDC/NHSN criteria. This fact is important because the plaintiffs' experts have repeatedly and erroneously equated the presence of a positive culture of removed mesh grafts as proof of the presence of infection. However, a positive culture of a removed prosthetic device can occur due to contamination during the removal of this device or during its transport to the laboratory. As discussed later in my report, this phenomenon is particularly likely to occur if the device is removed via an incision that involves a non-sterile area such as the vagina, but it can also occur in other settings such as during removal of a prosthetic heart valve or pacemaker wires.

Further, it is not clear, nor is it an established fact, that transient, superficial or even persistent vaginal erosions that may occur following the placement of a TVT device meet the definition of post-operative infection using the criteria discussed above. Indeed, in most cases, such erosions are not accompanied by other bona fide signs of infection such as purulence or significant signs of inflammation, and many erosions resolve with topical estrogen therapy. Although some individual surgeons may attribute these erosions to an infection, others clearly do not. The CDC/NSHN criteria referenced previously do not discuss this matter, nor are there, to

my knowledge, any widely-accepted, published criteria that define a superficial mesh erosion, particularly one that resolves without antibiotic therapy, as a post-operative infection.

b. Secondary infections

Any operative procedure can be associated with secondary infection complications. For example, urinary tract infections may occur secondary to placement of urinary catheters placed preoperatively, intraoperatively, or postoperatively. Vascular catheter-related bloodstream infections may occur secondary to intravenous devices used to administer intravenous fluids and medications. Lower respiratory tract infections may occur as complications secondary to tracheal intubation required for general anesthesia. Moreover, patients who undergo almost any surgical procedure can develop subsequent problems such as urinary tract infections, pneumonia, or yeast infections that occur months or years after surgery that are unrelated or completely incidental to their original surgery.

c. Evidence Based Medicine

As is common for many surgical procedures currently in use in modern practice, there are wide variations in the study designs of published papers that compare results in patients undergoing the implantation of a TVT device to outcomes in patients who undergo other surgical procedures to correct stress urinary incontinence. Many of the published studies about outcomes after traditional repairs are retrospective. Further, the methods used to define, detect, and then report various types of surgical complications and benefits vary widely. Also, the lengths of follow-up of many of the published studies that report outcomes after these surgical procedures are variable. However, despite the limitations of individual studies, information about outcomes and risks obtained from these studies often reveals a pattern and clinically useful information

that, when coupled with years of clinical experience by surgeons, allow physicians to make reasonable estimates and assessments of the relative risks and benefits *for individual patients*.

Because my expertise lies in matters related to post-operative infections, I will confine my subsequent remarks to issues related to post-operative infection following implantation of TVT devices in humans rather than experimental studies in laboratory animals or in vitro laboratory experiments. My discussion and analysis will utilize the CDC/NHSN definitions for postoperative surgical site infections discussed previously that are widely and nearly universally used by experts and researchers throughout the United States and the world. Specifically I will use these definitions to analyze and discuss published data on the risk of post-operative surgical site infections in the studies that report outcomes after surgery that use TVT.

B. TVT implants are not associated with a substantial or excessive risk of infection.

1. The overall risk of surgical infection following TVT placement is low and superior to the risk of surgical infection in traditional surgical treatments for stress urinary incontinence.

The overall rate of wound infection from the use of TVT implants is low, particularly in comparison to traditional surgical treatments for SUI. This opinion is supported by numerous individual comparative and noncomparative studies of the use of TVT mesh in women in various countries. For example, the risk of a postoperative wound (surgical site) infection was assessed in 5 comparative studies involving women in various countries who underwent placement of a TVT device and women who underwent a colposuspension procedure. (Paraiso 2004, Ward 2002, Martinez-Fornes 2009, El-Barky 2005, Valpas 2003). The occurrence of wound infection ranged from 0% (El-Barky 2005) to 13% (Martinez Fornes 2009) in women treated with a TVT device, and from 2% (Valpas 2003) to 8% (El-Barky 2005) in women undergoing colposuspensions. In fact, the risk of a postoperative wound infection was statistically higher in

women undergoing colposuspensions than in women undergoing placement of a TVT device in one of these studies (El-Barky 2005). The differences in rates of postoperative wound infections were not statistically significant in the other studies.

In 2014, Schimpf et al. conducted a systematic review and meta-analysis of these and other randomized controlled trials from 1990 through 2013 with a minimum 12 months of follow-up that compared the Burch colposuspension and the mid-urethral sling. [Schimpf et al., Sling surgery for stress urinary incontinence in women: a systematic review and meta-analysis, Am. J. Obstet. Gyne 2014, 210:1.e1.] Consistent with the above rates, the authors found that the rate of wound infections following the implantation of a retropubic mid-urethral sling (such as the TVT) ranged from 0% to 13% in 13 randomized controlled studies. From this, Schimpf et al. estimated that the rate of wound infections for TVT mid-urethral slings was just 0.75% and for TVT-O, 0.74%. By contrast, the authors concluded that the rate of wound infections following a Burch colposuspension was 7.0%. [Schimpf 1.e8.]

The Schimpf review and meta-analysis also included trials comparing the mid-urethral sling to the pubovaginal sling. Whereas the authors estimated a wound infection rate of 0.75% for the TVT mid-urethral sling and 0.74% for the TVT-O mid-urethral sling, they estimated that the rate of wound infection following the implantation of a pubovaginal sling to be 2.6%. [Schimpf 1.e8.] Based in part on this lower rate of wound infection, the authors supported the use of mid-urethral slings such as TVT over pubovaginal slings. [Schimpf 1.e19.]

In their 2015 Cochrane review assessing the clinical effects of mid-urethral sling operations for the treatment of SUI, Ford et al. summarized data from several large registries concerning the incidence of complications following retropubic and transobturator sling surgeries. [Ford et al., Mid-urethral sling operations for stress urinary incontinence in women

(Review), Cochrane Collaboration 2015.] The number of TVT procedures in these registries ranged from 809 to 4281, and the composite infection rate for retropubic slings was just 0.7% and for transobturator slings, 0.6%. [Ford 45.]

The evidence discussed above of low rates of infection is consistent with my own clinical and research experience. I have a longstanding interest in the problem of post-operative surgical site infections and more than 30 years of clinical experience as a hospital-based consultant and a hospital epidemiologist. I have not been able to find any published data suggesting that there is a higher rate of surgical site infections (defined by the rigorous and accepted criteria discussed above) following trans-vaginal SUI surgeries than in other pelvic or abdominal procedures for the treatment of SUI. Additionally, I am the Director of the Duke Infection Control Outreach Network, a consortium of 43 hospitals in Virginia, North Carolina, Georgia, West Virginia, Michigan and Florida. At no point, to my knowledge, has any member hospital raised any issue that trans-vaginal implantation of TVT devices causes a higher risk of post-operative pelvic infections.

The contention of Plaintiffs' experts that the TVT device is defective due to an alleged propensity to cause infections is also inconsistent with the position taken by several major medical organizations that have addressed this issue. As set forth below, these organizations recognize that the use of synthetic mid-urethral slings is the current standard treatment for SUI and that the safety and efficacy of the TVT device has been established through numerous clinical trials, the results of which are a logical and appropriate basis for the current preference for the widespread use of synthetic mid-urethral slings.

a. American Urogynecologic Society

The American Urogynecologic Society published a position statement concluding that synthetic mid-urethral slings are safe and effective relative to other treatment options. This position statement unambiguously states that these synthetic devices are now the gold standard for surgical treatment of stress urinary incontinence:

> Since the publication of numerous level one randomized comparative trials, the MUS [mid-urethral sling] has become the most common surgical procedure for the treatment of SUI in the US and the developed world. This procedure has essentially replaced open and transvaginal suspension surgeries for uncomplicated SUI. There have been over 100 surgical procedures developed for the management of SUI and there is now adequate evidence that the MUS is associated with less pain, shorter hospitalization, faster return to usual activities, and reduced costs as compared to historic options that have been used to treat SUI over the past century. Full-length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard for stress incontinence surgery. Over 3 million MUS have been placed worldwide and a recent survey indicates that these procedures are used by >99% of AUGS members. (citations omitted).

[American Urogynecologic Society, Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence (January 2014)].

b. American Urological Association

Similarly, the American Urological Association states in its "AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence" that:

> Multiple case series and randomized controlled trials attest to the efficacy of synthetic polypropylene mesh slings at 5-10 years. This efficacy is equivalent or superior to other surgical techniques. There is no significant increase in adverse events observed over this period of follow-up. Based on these data, the AUA Guideline for the Surgical Management of Stress Urinary Incontinence (2009) concluded that synthetic slings are an appropriate treatment choice for women with stress incontinence, with similar efficacy but less morbidity than conventional non-mesh sling techniques.

[AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence (November 2011)].

c. EAU Guidelines

The European Association of Urology published its guidelines on urinary incontinence in September 2012 and concluded: "There has been a rapid adoption of mid-urethral synthetic sling insertion as the first-line surgical option for SUI because it is effective, it is less invasive, and patients recover more quickly." The EAU Guidelines also state that a "systematic review compared mid-urethral slings with both open colposuspension (nine trials) and laparoscopic colposuspension (eight trials). Retropubic insertion of a synthetic midurethral sling gave equivalent patient-reported and superior clinician-reported cure of SUI compared with colposuspension at 12 mo[nths]." The report also found lower rates of de novo urge incontinence and voiding dysfunction with synthetic slings as opposed to colposuspension. [EAU Guidelines on Surgical Treatment of Urinary Incontinence, Eur. Urology 62 (2012) 1118-1129]. The Guidelines ultimately conclude that midurethral slings should be the first line of surgical intervention. [Id.]

d. NICE Guidelines

Finally, the United Kingdom's National Institute for Health Care & Excellence [NICE] Guidelines expressly state that the TVT procedure is supported by high-quality evidence of efficacy and safety and supported by robust RCT evidence. [NICE Guideline 1.10.3, n.11].

2. Urinary Tract Infections

a. Background

Urinary tract infections in women are exceptionally common; it is estimated that on a global basis, 150 million UTIs occur annually. [Raz, Recurrent Urinary Tract Infections in Postmenopausal Women, Clin Inf D, 2000;30:152-6]. In fact, UTIs are the most common bacterial infection. For example, in 1997, the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey estimated that UTIs accounted for 7 million office visits and 1 million emergency department visits. [Foxman, Epidemiology of Urinary tract infections: incidence, morbidity, and economic costs, Am J Med, 2002 Jul 8; 113 Suppl 1A: 5S-13S]. Catheter-associated UTIs are the most common nosocomial infection, accounting for more than a million cases in hospitals and nursing homes. [Foxman]. Fortunately, UTIs are typically minor, typically responsive to antibiotic therapy, and usually do not present a serious risk to the patient.

b. Risk Factors

There are numerous genetic, biological, behavioral, anatomical, and age-related factors that increase a person's risk for contracting a UTI. For example, women are more likely than men to suffer from UTIs, and post-menopausal women are more likely than pre-menopausal women to contract a UTI. A patient who undergoes any surgery in which a catheter is placed is more likely to develop a subsequent UTI than a surgical patient who is not catheterized. A person who has previously suffered from a UTI is more likely to contract a subsequent UTI. And, particularly relevant to this litigation given that the TVT product is indicated for use in women who suffer from SUI, women who suffer from incontinence are dramatically more likely

to contract a UTI than women who do not suffer from incontinence [OR 5.79]. [Raz]; [Up To Date, Recurrent urinary tract infections in women, p. 3 of 17].

Thus, any discussion of the risks of developing a UTI following implantation of a TVT device must start from the premise that the population undergoing TVT implantation (women, mostly post-menopausal, suffering from incontinence) is peculiarly susceptible to UTIs, irrespective of the treatment option selected to address the incontinence.

c. Diagnostic Criteria

It is common for urine samples to be contaminated with microorganisms during the collection of urine. In order to confirm the diagnosis of a urinary tract infection, patients must have: (1) typical symptoms of a urinary tract infection, such as burning and cloudy urine; (2) pyuria (detected by either direct urine microscopy or indirectly by simple tests such as a positive leucocyte esterase test) and/or a positive nitrite test and (3) a positive urine culture. The threshold for determining a positive urine culture is dependent on how the urine sample is obtained. A colony count of 10^2 colony forming units/ml or greater is typically considered significant if the sample is obtained via a urinary catheter; a colony count of 10^5 colony forming units/ml or greater is typically but not invariably considered significant if the same is obtained by a "clean catch" sample of voided urine.

Additionally, bacterial infections in patients with urinary tract infections are typically and characteristically monomicrobial. The growth of multiple bacterial or fungal organisms from a properly collected urine sample is typically and routinely attributed to extrinsic contamination. However, such contamination can and frequently does occur because improper handling or delays in processing urine samples or because of improper collection of a urine sample from

individual patients. Although the finding of multiple pathogens in a properly collected urine sample is considered to be a non-diagnostic laboratory result, such a finding cannot be used to completely exclude a diagnosis of a urinary tract infection. In other words, the finding of a contaminated (multi-microbial) urine sample cannot completely exclude a diagnosis of a UTI. Thus clinicians must consider other factors, such as whether clinical signs and/or symptoms, or the clinical scenario indicate the likely presence of a UTI when they assess the clinical significance of a laboratory report showing a contaminated urine sample.

d. Placement of the TVT does not Create an Excessive Risk of UTI

Studies have shown that the risk of urinary tract infections following the surgical treatment of SUI is similar across patient populations. For example, the authors of a study published in 2010 that analyzed previously published studies reporting on the risk of urinary tract infections in women undergoing colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence found no difference in the rate of urinary tract infections in women undergoing TVT placement as compared to those undergoing a Burch colposuspension. The actual rate of urinary tract infections ranged from 0% (in 3 of 7 individual studies) to a high of 5.7% (in one study) for 469 women undergoing implantation of a TVT device to 0% (in 2 of 7 studies) to a high of 8.6% (in one study) of a total 454 women undergoing a Burch procedure. [European Urology 2010: 58: 218-238]. Other studies, including the Schimpf meta-analysis, have reported that the risk of postoperative urinary tract infections in women undergoing TVT device placement have ranged from 0-22%; in contrast, the risk of urinary tract infections in women undergoing colposuspension procedures has ranged from 0-32% in individual studies. **[**Paraiso 2004, Ward 2002, Martinez-Fornes 2009, El-Barky 2005,

Valpas 2003, Liapis 2002**];** [see also Albo et al., Treatment success of retropubic and transobturator mid urethral slings at 24 months, J of Urology 2012; 188: 2281-87; Albo et al., Burch colposuspension versus fascial sling to reduce urinary stress incontinence, N Engl J Med 2007; 356: 2143-55]**.**

The preceding data on the relative risks of urinary tract infections should be placed in perspective in comparison to the risk of urinary tract infections following other types of pelvic surgery. For example, one recent study showed the risk of postoperative urinary tract infections was 30.7% in women undergoing surgery for gynecological cancer. [Crosby-Nwaobi RR, Faithfull S High risk of urinary tract infection in post-operative gynecology patients: a retrospective case analysis Eur J Cancer Care 2011: 20: 825-31]. As another example, the risk of developing a postoperative urinary tract infection after surgery was 6% in another large study involving 93,931 patients with colorectal cancer. [Kang CY et al. Risk factors for postoperative urinary tract infection and urinary retention in patients undergoing surgery for colorectal cancer**.** Am Surg. 2012 78:1100-4].

Moreover, as discussed above, the data regarding the relative risks of urinary tract infections must be considered relative to the yearly incidence of UTIs in the same general population. In a multicenter randomized clinical trial comparing TVT and Ethicon's transobturator tension-free vaginal tape (TVT-O), Laurikainen et al. reported that 20.6% of the TVT group had at least one episode of a UTI that required treatment with antibiotics. The authors noted, however, that the yearly incidence of UTI in a normal population of the same age as the women of the present trial has been found to be as high as 10-20%. The authors thus concluded that an incidence of 21% during a two-year follow up did not differ from the incidence of UTI in a normal population. [Laurikainen et al., Five-year results of a randomized

trial comparing retropubic and transobturator midurethral slings for stress incontinence, Euro. Assoc. of Urology, 2014].

Thus, the placement of TVT does not present an excessive risk of UTI, nor is the rate of UTI associated with TVT higher than that associated with other surgical treatments for SUI.

3. Vaginal Infections

Vaginal yeast infections are common. Indeed it is likely that millions of American women have minor yeast infections every year. These minor vaginal yeast infections commonly occur following the administration of oral antibiotic therapy given for routine reasons such as treatment of upper respiratory tract infections. To my knowledge there are no studies that show that women who undergo transvaginal surgery with mesh grafts have a higher rate of vaginal yeast infections than women undergoing other types of pelvic surgery or other surgical procedures to correct stress urinary incontinence.

C. Rebuttal of Other Issues Raised by Plaintiffs' Experts

1. Vaginal surgical procedures are not intrinsically unsafe

In their reports, Drs. Klinge (8) and Rosenzweig (27) state that surgical procedures involving TVT devices are subject to increased risk or are unsafe due to the fact that the devices are implanted trans-vaginally and that this trans-vaginal implantation may cause an excessive infection risk.

First, neither Dr. Klinge nor Dr. Rosenzweig is an infectious disease doctor. Second, although trans-vaginal placement of a mesh graft is undoubtedly accompanied by procedure-related contamination due to bacteria and other microorganisms normally present on the mucosal surfaces of the vagina or on the skin of the perineum, this is not inherently, excessively, or

prohibitively dangerous. Humans have an array of intrinsic host immune mechanisms that are highly effective against infection. For example, vaginal tissues are highly vascularized and intrinsically quite resistant to infection. Indeed, surgical procedures such as vaginal hysterectomy and diagnostic and therapeutic procedures are routinely performed via a trans-vaginal approach. And hundreds of millions of women who give birth each year incur minor and even major disruptions of their vaginal tissues, yet only a small percentage develops serious infections. In many cases, instruments such as laparoscopes are safely placed through vaginal tissues. Contamination with microorganisms predictably occurs in such circumstances and during such procedures, yet infection is a relatively uncommon complication.

The contention of the plaintiffs' experts is that, because trans-vaginal surgery is Class II (clean-contaminated), there is a higher risk of infection from trans-vaginal surgery than for SUI repairs involving the abdomen because the latter surgeries are usually, but not invariably, Class I (clean) procedures. This contention, although theoretically possible, does not actually occur for the reasons cited previously and because of the data from the studies that I cited above. Plaintiffs' experts do not cite clinically relevant literature to support their claim that trans-vaginal surgery has a higher rate of infection than open surgical procedures involving mesh grafts. To the best of my knowledge, there is no literature that supports their point of view. In fact, the infection rate for TVT is lower than colposuspension (see above).

Dr. Rosenzweig cites data from a 2009 study by Vollebregt as a basis for the contention that frequent contamination of vaginal mesh grafts makes this product inherently hazardous. Dr. Rosenzweig further states that this contamination may in turn produce "secondary-mesh related infections" that are localized around the mesh (page 28). In fact, Vollebregt and colleagues found **no** clinical signs of infection in the vaginal mesh grafts implanted in the 67 women studied

in this report despite follow-ups for a minimum duration of 6 months in all patients. Vollebregt et al. also noted that, although rates of bacterial colonization were high, the density of this colonization was "below what is known as clinical (sic) important contamination." Vollebregt further explained that the density of colonization observed in the grafts used in this study was far less than the threshold used by other experts to define "contamination" (*i.e.*, 5000 CFU/ml or greater). [Culligan P, et al., Bacterial colony counts during vaginal surgery, Infect Dis Obstet Gynecol, 1996; 175: 11; 165).] Vollebregt and colleagues further stated that "none of the [mesh graft] colonisations we found can be regarded as contamination."

Drs. Vollebregt and colleagues also discuss several interesting aspects of the outcomes of the patients in the preceding study that were not mentioned or acknowledged by Plaintiffs' experts, including two important observations. First, Dr. Vollebregt et al. noted that no clinical infections were found during a prospective duration of follow-up of 6 months in their 67-patient cohort, a finding the authors noted "*is consistent with literature that shows the mesh-related infections occur infrequently (0-8%) in vaginal pelvic organ prolapse surgery*" (page 1351 of the Vollebregt paper). Second, Vollebregt et al. hypothesized that "delayed wound healing" rather than infection was the actual cause of the mesh erosion/exposure that was observed in 3 of 67 women in this prospective study. Vollebregt and colleagues based this opinion on the following statement: "*Since all exposures occurred in the line of incision, and intraoperative cultures of the removed mesh in these women were either negative or showed non-pathogenic bacteria in low densities, we believe that delayed wound healing was the cause of this mesh exposure in our series*."

Vollebregt et al. also cited data from other studies to support this opinion. Specifically, they discussed a paper by Boulanger and colleagues that analyzed the results of bacterial cultures

of mesh material taken from 16 women who underwent removal of their vaginal mesh due to erosion or infection. Cultures of graft material from these 16 women with erosions revealed bacteria quantities below 10^3/ml. [Boulanger L, et al., Bacteriological analysis of meshes removed for complications after surgical management of urinary incontinence or pelvic organ prolapse. Int Ureogynecol J 2008:19: 827-31]. I agree with the following comment by Vollebregt et al. made about the findings in this study "*Whether or not these erosions were due to contamination during initial surgery remains unclear, but this seems highly unlikely in view of our data showing that low-grade contamination occurs during surgery very frequently. If a causal relationship [between contamination and erosion] should exist, we would have expected much more problems of infection or erosion in our series*." Furthermore, Boulanger et al. admitted that *"the collection methodology we used was not validated.*" Indeed, it is quite possible that the low-level contamination the authors observed could have been due to or confounded by contamination with vaginal flora during the actual trans-vaginal removal of the mesh material. In addition, the quantitative methods utilized to estimate the bacterial burden on these non-randomly selected materials was imprecise and non-standardized. The authors made no effort to demonstrate that their results were reproducible by testing multiple samples.

Dr. Rosenzweig also cites to an abstract by Shah et al. as an example of "numerous peer-reviewed journal articles regarding secondary-mesh related infections as well as the dangers of implanting surgical mesh in a clean/contaminated field" (page 28). First, the Shah abstract is just that: an abstract. It is not a peer-reviewed article and, to my knowledge, was never published. Data presented at a meeting in abstract form, as the Shah data was, must be peer reviewed before it can be considered any level of evidence. Second, the Shah data are not statistically significant. Shah and colleagues examined a prospectively maintained database of only 50 patients who

presented with mesh-related complications. And third, the Shah abstract fails to include any discussion of methods, such as how each sample was processed. For each of these reasons, the Shah abstract in no way supports Dr. Rosenzweig's statement that "numerous peer-reviewed journal articles regarding secondary-mesh related infections as well as the dangers of implanting surgical mesh in a clean/contaminated field."

2. There is no convincing clinical data in humans that trans-vaginally placed mesh produces biofilms that frequently or commonly result in so-called "sub-clinical" or "chronic infections" that in turn cause chronic pain and late complications.

Dr. Klinge states that, because of the formation of a biofilm, an infection may develop on transvaginally-implanted mesh several years after implantation. For support, however, he cites a dog study he and his colleagues conducted and a 1998 study he authored on the repair of abdominal wall hernias. Dr. Klinge does not cite evidence from his prior publications that is in variance with the comments in his expert report. For example, in 2002, Dr. Klinge wrote the following in a published paper in which he studied the risk of persistence of a virulent organism (S. aureus) in experiments in which different types of contaminated mesh materials were implanted into rats that were sacrificed and their mesh grafts examined histologically and bacteriologically 7 days later. "*Biomaterials are thought to increase the infection rate, though this could not be proven in several clinical trials.*[1-4] *Even in highly sterile alloarthroplastic operations bacterial colonialization [sic] has been observed in about 40% of cases.*[5] *Additionally, local fluid collections such as hematoma or seroma formation can favor the development of a manifest bacterial infection. The risk might rise in the case of small niches, of an incomplete ingrowth of tissue, or of markedly hydrophobic foreign materials, preventing close contact of the cells to the foreign-body surface. However, the published experimental data are*

overall contradictory. . ." [Do Multifilament Alloplastic Meshes Increase the Infection Rate? Analysis of the Polymeric Surface, the Bacteria Adherence, and the In Vivo Consequences in a Rat Model U. Klinge, K. Junge, B. Spellerberg, C. Piroth, B. Klosterhalfen, V. Schumpelick].

Although biofilms can indeed form on virtually any avascular or poorly vascularized surface or implanted prosthetic material, the formation of a biofilm is not invariable when a foreign body is implanted even in the face of contamination, as supported by the quote from Dr. Klinge's publications cited above. There are many examples in clinical medicine suggesting that the intraoperative contamination during implantation of a prosthetic device may occur yet biofilm formation and subsequent chronic infection and late complications are rare. For example, thousands of patients with open fractures require bony fixation using metal pins, plates and screws. Although biofilms with or without late-onset infections may occur in such situations, the majority of patients do not develop early or delayed infections weeks, months, or years later. Similarly, other prosthetic materials (cochlear implants, ocular lenses) are commonly placed under conditions in which complete antisepsis cannot be assured and in which some degree of bacterial contamination probably occurs yet clinically apparent or significant infection in such circumstances are uncommon. Finally, none of the plaintiffs' experts attempt to explain why the overwhelming majority of women undergoing implantation of TVT devices do not develop either wound infections or late-onset complications. The Plaintiffs' experts selectively cite in vitro or animal studies to support their theory, yet they do not discuss how or why the majority of women undergoing implantation of TVT devices do not develop infections [see previous discussion about the risk of infection after TVT device placement].

3. Late Onset Infection and Complications

I disagree with Dr. Klinge's comments that a patient implanted with a TVT device is likely to develop a mesh-related infection or other complications years after the mesh has been implanted due to bacteria that might adhere to the mesh. Dr. Klinge cites no clinical or published data to support this statement. Again, during my clinical career of more than 35 years, I have seen more than 20,000 patients with infections in consultation. These consultations have included thousands of patients with infections that have developed after surgical implantation of prosthetic valves, joints, pacemakers, vascular grafts, mesh grafts and orthopedic hardware. My experience confirms the well-known clinical fact that infections of implanted prosthetic devices uncommonly appear more than 1 year after surgical implantation. And importantly, the vast majority of such delayed-onset infections of prosthetic materials are due to obvious causes unrelated to their original surgical implantation, such as infections of the bloodstream or new infections in tissues or structures contiguous to the implanted prosthetic material.

Nor is Dr. Klinge's theory about late-onset infections or other complications supported by the medical literature. In this case, I have consulted with Dr. David J. Weber, who is a board-certified epidemiologist at the University of North Carolina at Chapel Hill. The purpose of this consultation was to rely on Dr. Weber's expertise in matters related to the design, outcomes, and validity of scientific studies that have evaluated outcomes of women undergoing implantation of a TVT. Dr. Weber and I are co-investigators in epidemiological studies related to the Duke-UNC epidemiological research center, which is funded by a grant from the Centers for Disease Control. In addition, Dr. Weber has served as a mentor and research co-supervisor for many of my trainees who obtained a Masters in Public Health Degree while performing research at Duke University Medical Center and in DICON under my direct supervision. Dr. Weber and his

colleagues at UNC undertook a comprehensive review of the published literature examining the outcomes of women undergoing TVT implantation in comparative and non-comparative clinical studies, including meta-analyses of the same.

Dr. Weber identified 15 papers, all of which were either prospective cohort studies or clinical trials. [See Long-Term Studies table below.] The studies involved different surgeons and different patient populations and were conducted in many different countries or regions. The number of subjects evaluated in the studies ranged from 12 (Abdul-Rahman 2010) to 483 (Svenningsen 2013). Smaller numbers of subjects may have been available for some follow-up measures. Follow-up times ranged from a mean or median of 36 months (Wu 2010) to 201 months (Nilsson 2013). Seven studies had a follow-up time of 10 or more years.

The long-term outcomes studies identified by Dr. Weber and colleagues confirmed that, contrary to Dr. Klinge's speculation, TVT is not associated with significant late-onset complications. In fact, the authors of 11 of the studies stated that TVT demonstrated an excellent long-term track record, and several of the authors noted that TVT had a low frequency of complications. These studies contradict the theory that complications are manifesting years after TVT implantation. Also infection-related complications were particularly low in the preceding review of long-term outcome studies. In the Wu 2010 study, the frequency of wound infection was reported as 0% (0 infections out of 105 patients). In the Svenningsen 2013 study, there were 3 superficial wound infections (0.6%; 3 infections out of 483 patients) and 4 deep infections (0.8%; 4 infections out of 483 patients). Six studies reported on urinary tract infections (Liapis 2008, Olsson 2010, Wu 2010, Svenningsen 2013, Laurikainen 2014, and Kenton 2015), and rates were generally low. The frequency of urinary tract infections in these studies ranged from 2.3% (Svenningsen 2013) to 20.6% (Laurikainen 2015, which defined a urinary tract infection as at

least one episode over 5 years treated with antibiotics). However, in the absence of a comparative group, it is impossible to assess whether TVT surgery had a role in these infections, since urinary tract infections are common among women, especially as they age.

In short, there is overwhelming evidence that TVT patients are not subject to a clinically significant higher risk of developing late-onset infections or other complications than patients who undergo alternative surgical procedures. Although I do not deny that a late-onset complication can occur, the same can be said of any medical procedure. In the case of the TVT, the risk of late-onset complications is extraordinarily small and is certainly outweighed by the life-changing benefits enjoyed by the hundreds of thousands of women who have been able to resume their normal lives free of SUI. These long-term studies—in which nearly 1,300 patients were available for follow-up—contradict Dr. Klinge's opinion that TVT patients are subject to a high risk of developing infections and other complications several years after implantation due to "contamination" of the mesh. The data in the preceding long-term studies support the position taken by the several major medical organizations referenced above that TVT is safe for long term use.

4. Mesh Design

Several of plaintiffs' experts discuss in their various reports a number of design-related issues that they contend relate to infection issues in actual patients. Dr. Rosenweig, for example, opines that TVT is characterized by degradation of the mesh, chronic foreign body reaction, fraying and particle loss, roping and curling of the mesh, loss of pore size, fibrotic bridging, and mesh contracture. He states in his report that these characteristics cause "a multitude of injuries," including wound infection.

I am not an expert in pelvic mesh design, degradation and particle loss, fibrotic bridging, effective porosity, erosion, or shrinkage and contracture, and, therefore, will not be addressing the substance of these topics. However, as an expert in infectious diseases, I disagree that the alleged design-related issues raise infection risks in actual patients. As stated above, there is no clinical evidence that these alleged defects cause infections in actual patients. Indeed, as explained previously, the infection rate in women undergoing implantation of TVT devices is low and this risk is equal to or lower than the infection rate of the prior gold standard procedure for correction of stress urinary incontinence, the Burch colposuspension, and either similarly low or lower than the risk of infection in other common procedures involving implantation of prosthetic materials. Simply put, in the absence of any published data showing that implantation of TVT devices results in statistically significantly elevated rates of clinically apparent and clinically relevant infections, the issues about mesh design, degradation, and effective porosity raised by the plaintiffs' experts provide no basis for an allegation that the TVT devices cause unacceptable risks of infection in women.

_____

Daniel J. Sexton, M.D.
Duke University
Durham, NC 27708

LONG-TERM STUDIES

Author	Date	Ref.	Type	No. of Patients	Follow-Up	Frequency of Infections
Abdul-Rahman	2010	BJU Int. 2010; 106:827-30	Pros. Cohort	9	10 year mean	Not reported
Aigmueller	2014	Int. Urogyn. J.	Pros. Cohort	174	10 years	Not reported
Song	2009	BJU Int. 2009; 104:1113-7	Pros. Cohort	306	92.3 months (range 84-110)	Not reported
Wu	2010	Int. Urogyn. J 2010; 21:645-649	Non-random Comparative	105	3 years mean	SSI (postop) – 0/105 (0.0%) UTI – 5/105 (4.8%)
Zugor	2010	Int. Urol Nephrol 2010; 42:915-920	Non-random Comparative	100	48 months median	Not reported
Angioli	2010	Euro. Urology 2010; 58:671-677	RCT	35	60 months	Not reported
Li	2012	J. Minimally Invasive Gyn. 2012; 19:201-5	Pros. Cohort	55	6.8 years (range 62-102 months)	Not reported
Liapis	2008	Int. Urogyn. J 2008; 19:1509-1512	Pros. Cohort	61	7 years	UTI – 2/61 (3.2%)
Nilsson	2013	Int. Urogyn. J. 2013: epub	Pros. Cohort	46	201 months mean	Not reported
Olsson	2010	Int. Urogyn. J. 2010; 21:679-683	Pros. Cohort	124	138 months median	UTI – 9/124 (7.2%)
Serati	2012	Euro. Urology 61:939-946	Pros. Cohort	58	120 months	Not reported

LONG-TERM STUDIES

Svenningsen	2013	Int. Urogyn. J. 2013: epub	Pros. Cohort	483	Postoperative	Superficial SSI (postop) – 3/483 (0.6%) Deep SSI (postop) – 4/483 (0.8%) Recurrent UTI – 11/471 (2.3%)
Laurikainen	2014	Euro. Urology	RCT	268	60 months	UTI (at least one episode treated with antibiotics) – 27/131 (20.6%)
Kenton	2015	J. Urology	Pros. Cohort (following pt. in original RCT)	404	60 months	Recurrent UTI requiring intervention – 4/201 (2%) Non-serious recurrent UTI – 17/201 (8%)
Khan	2015	BJU International	RCT	201	10 years	Not reported